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Review

Treatment and prevention strategies for the COVID 19 pandemic: A review of immunotherapeutic approaches for neutralizing SARS-CoV-2

Pravas Kumar Baral, Jiang Yin, Michael N.G. James *

Department of Biochemistry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G 2H7, Canada

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ABSTRACT

Researchers from the world over are working to create prophylactic and therapeutic interventions to combat the COVID-19 global healthcare crisis. The current therapeutic options against the COVID-19 include repurposed drugs aimed at targets other than virus-specific proteins. Antibody-based therapeutics carry a lot of promise, and there are several of these candidates for COVID-19 treatment currently being investigated in the preclinical and clinical research stages around the world. The viral spike protein (S protein) appears to be the main target of antibody development candidates, with the majority being monoclonal antibodies. Several antibody candidates targeting the SARS-CoV-2 S protein include LY-CoV555, REGN-COV2, JS016, TY027, CT-P59, BRII-196, BRII-198 and SCTA01. These neutralizing antibodies will treat COVID-19 and possibly future coronavirus infections. Future studies should focus on effective immune-therapeutics and immunomodulators with the purpose of developing specific, affordable, and cost-effective prophylactic and treatment regimens to fight the COVID-19 globally.

SARS-CoV-2 is the virus responsible for coronavirus disease 2019 (COVID-19); it is a single-stranded RNA betacoronavirus first identified in Wuhan, China in December 2019 [1–3]. SARS-CoV-2 is the third lethal virus in the group; the other two virulent beta coronaviruses, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), have higher fatality rates than the SARS-CoV-2 [4]. SARS-CoV-2, on the other hand, seems to have a higher transmission rate and therefore a larger distribution around the world, infecting more than 138 million people to date. The origins of the SARS-CoV-2 virus are still unknown. The presence of a similar coronavirus, RaTG13, in bats, suggests that the virus may be transmitted to humans from its native host during close contact. The molecular events that trigger SARS-CoV-2 transmission from bats to humans, on the other hand, must be verified. While the other respiratory tract viruses in this genus only induce moderate cold symptoms, SARS-CoV-2 has the potential to become highly virulent in 1-2% of the population, resulting in severe pneumonia-like symptoms and death. The bulk of patients who contract the infection experience milder symptoms such as a cold, sore throat, cough, runny nose, throat inflammation, and fever. A large portion of the infected population is still asymptomatic [2]. SARS-CoV-2 has resulted in many more outbreaks, deaths, and economic disruptions than SARS-CoV did between the years 2002 and 2003 [5]. The impact of the coronavirus disease pandemic on physical and mental health, the economy, and many aspects of social life have been enormous; 2.85 million lives have been lost to date and there is no sign of the virus being contained. The coronavirus disease pandemic (COVID-19) has rapidly spread to almost every country and territory on the planet.

The urgency of this threat has prompted scientists in many countries to seek solutions through drug repurposing and repositioning of previously approved drugs, as well as fast-tracking of vaccine and new drug development. Some of the repurposed candidate drugs, on the other hand, have already failed in clinical trials [6]. Antiviral drugs developed for other similar viruses have been suggested as possible inhibitors of virus cell entry or replication. Supporting the immune system's ability to function properly and fight the virus, on the other hand, is a viable strategy. In the final stages of the disease, normalization or even suppression of dysregulated immune responses may be required.

1. Pathogenesis of SARS-CoV-2 in brief

SARS-CoV-2 gains entry to the lungs through the nasopharyngeal mucosal membrane and subsequently targets the alveolar macrophages and the type I and II epithelial cells of the lungs [7]. The coronavirus

* Corresponding author.
E-mail address: michael.james@ualberta.ca (M.N.G. James).

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genome encodes four proteins responsible for the structure of complete viral particles called a virion; these are surface spike (S) glycoprotein, membrane (M) protein, small envelope (E) glycoprotein, and nucleocapsid (N) protein (Fig. 1). Interaction of the spike S protein of the SARS-CoV-2 with the host epithelial angiotensin-converting enzyme 2 (ACE2) is the leading event for the viral entry; the serine protease called TMPRSS2 (transmembrane protease, serine 2) or Cathepsin L/B (CTSL/B) seem to facilitate the process of host entry [8]. Clathrin-dependent and -independent endocytosis pathways are alternate routes by which the virus can gain entry to the host cell [9]. After gaining entry into the cytoplasm, SARS-CoV-2 utilizes the JAK-STAT pathway to target the lymphocytes. Increase in body temperature, non-productive cough, dyspnea, malaise, fatigue, lymphopenia, and pneumonia are the symptoms exhibited by the patient after 2–14 days following viral exposure. The severity of these symptoms varies greatly from mild to severely infected patients. Laboratory test results indicate leucopenia, elevated C-reactive protein (CRP), and higher erythrocyte sedimentation rate (ESR) in the COVID-19 patients. In some instances, after the first episode of 7-14 days of initial symptoms of the disease, the virus may cause a second aggravated attack with severe pneumonia, ground-glass opacity, acute cardiac injury, and RNA anemia [10]. Apart from the lungs, other vital organs seem to be seriously affected by the second attack such as the heart, eyes, nose, brain, pancreas, kidney, and bladder. Patients who succumb to this deadly infection show an elevated level of neutrophil, D-dimer, blood urea nitrogen (BUN), and creatinine than do the survivors [11,12].

2. Immunotherapeutic approaches against SARS-CoV-2 based on its immunopathology

In seriously ill COVID-19 patients, the immune system is severely compromised [13]. The major cause is acute respiratory distress syndrome (ARDS), which induces lung damage and multiple organ failure, mediated by cytokine surge [14,15]. Corticosteroids or Janus kinase (JAK) inhibitors are treatment options considered for severely ill hospitalized COVID-19 patients [16]. However, the use of immunomodulatory interventions in the treatment of COVID-19 infection is also a point of contention [17]. In patients with a severe viral infection, general or systemic immunosuppression may not be necessary; the benefits of anti-inflammatory effects should be weighed against the risks of inhibiting immune response, that may hinder virus clearance and prolong disease [17]. Different experiments in humans and animals have shown that corticosteroid immunosuppression (both inhaled and systemic) reduces the induction of antiviral type-I interferon responses to a variety of respiratory viruses [18], a scenario that is likely to occur in the case of COVID-19. Selective JAK inhibitor treatments are supposed to have comparable outcomes. The type-I interferon pathway relies heavily on JAK-STAT signaling. Interferon activity has been shown to be inhibited by tofacitinib in vitro [19]. Interferon or other mediators (e.g., interleukin-6) suppression can also induce secondary bacterial infection, complicating the disease's path [20]. The decision to use immunosuppressive pharmacology to a chronically ill COVID-19 patient is also challenging. Potentially beneficial benefits of suppressing inflammation should be closely balanced against the risk of impairment of the immune system. In response to COVID-19, multiple immune cell types and inflammatory mediators including interleukin IL-1, IL-6, IL-12, IL17, IL-18, IL-22, IL-33, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) become hyper-activated [1,13,21]. Given the known role of cytokine dysregulation in causing this hyper inflammation, especially in the lungs, existing drugs targeting these mediators are being repurposed for the treatment of COVID-19. Rather than aiming at disrupting the virus lifecycle, molecules that target the host immune system were repurposed to treat COVID-19, apparently alleviating symptoms like cytokine storm and inflammation [22]. IL-6 antagonists levilimab, tocilizumab, sarilumab, olokizumab, and siltuximab, are being studied against COVID-19 [23]. Given the immune system's function in host defence, immunomodulation may be a viable technique for combating COVID-19, particularly when considering the patient's immune system's condition at different stages of the disease. Therefore, immunomodulatory interventions, such as vaccinations, interferons, convalescent plasma, anti-inflammatory drugs, antibodies, and other immunomodulators form the majority of promising approach for treating COVID-19 infection.

2.1. Active immunization using vaccines

Active immunization through vaccines is thought to be as the ultimate protection for saving the public from this novel virus; once vaccinated this will trigger the body to produce antibodies to resist this infection. Soon after finding the SARS-CoV-2 virus genetic sequence,

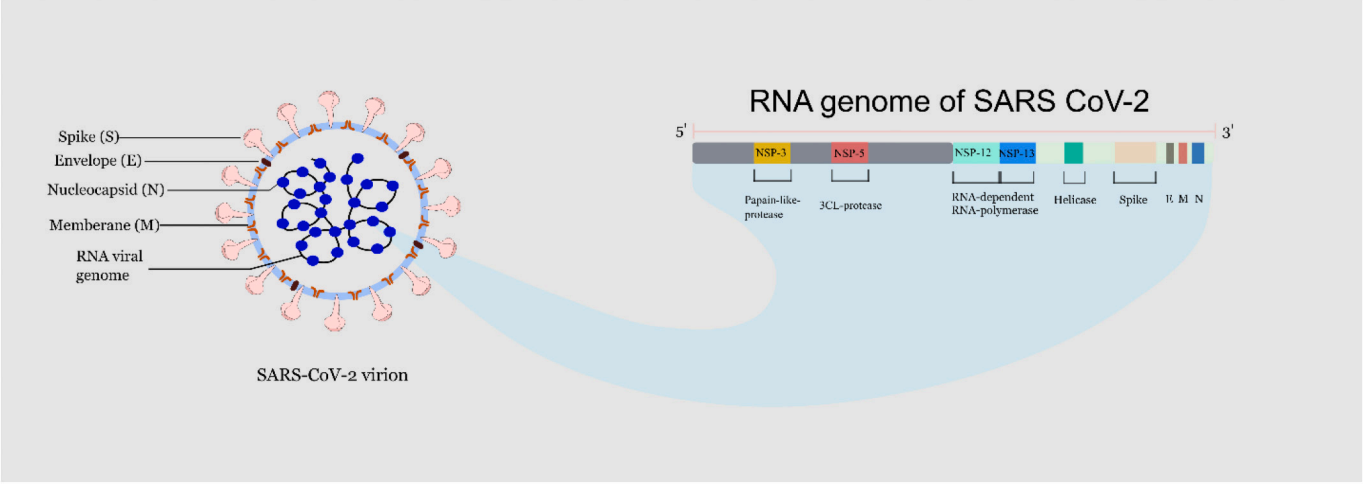

Fig. 1. Structure and genome organization of SARS-CoV-2. Close to two thirds of the single viral RNA genome encodes two large genes, ORF1a (yellow), ORF1b (blue), those encode 16 non-structural proteins (NSP1–NSP16), whereas the remaining genome encodes mostly the structural proteins that assemble into the progeny virion such as spike (S), envelope (E), layer (M), and nucleocapsid (N), featured in green. The NSPs form a membranous replication–transcription complex (RTC) that carries out genome transcription and replication. NSP5 and Part of NSP3 encode the 3CL-protease and the Papain-like protease (PLpro), respectively. These essential viral enzymes perform specific polypeptide cleavages in the pp1a and pp1b polyproteins to release individual functional viral proteins. Nsp3 is also critically involved in virus-host antagonism such as blocking the host innate immune response. NSP12 encodes the viral RNA-dependent RNA polymerase (RdRp) and NSP15 encodes the viral RNA helicase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

vaccine developments were fast-tracked at an unprecedented speed by several research groups and pharmaceutical companies. Huge funding investments have been dedicated by several government agencies considering the urgency and severity of the situation aroused by the pandemic [24]. There are plenty of vaccine candidates at various stages of development; to date, 29 candidate vaccines have entered the clinical phase, eight of which are already in phase 2 or 3. Additionally, more than 138 vaccine candidates are in the preclinical development stage waiting to enter the clinical trial stage. Different types of platforms have been employed in developing these investigational vaccines; these include inactivated, killed, or weakened pathogen, non-replicating viral vector, RNA, DNA, VLP (virus-like particle), and protein subunit structures of the SARS-CoV-2 [25]. Each of these platforms used in vaccine development has its own merits and demerits none of the techniques is completely flawless. DNA and RNA vaccines are preferred because of their rapid development, easy production, and safety, but scale-up for a large-scale production has been challenging. Viral particles are also a good option for scalable production but lack the full-scale immunogenicity advantages of a DNA and RNA virus. There are also other challenges associated with vaccine development such as adjuvants, dosage amount, and the number of required dosages to activate host immunity. These challenges need to be addressed prior to commencing a large-scale vaccination of the general population [26]. The vaccine candidates also need to be completed the clinical trials to exhibit full efficacy and safety before it is marketed to the public. Two mRNA-based vaccines developed by Pfizer-BioNTech and Moderna received FDA approval with efficacy rates of 95% and 94.1%, respectively; one adenovirus vectored vaccine ChAdOx1 to-19 (AZD1222) developed by Oxford-AstraZeneca received approval with a 70.4% efficacy rate; and finally, one inactivated virus vaccine developed by Sinopharm received approval with a 70.4% efficacy rate [27,27–29]. While these vaccines have been licensed for mass vaccination, questions about their long-term efficacy, any vaccine-related adverse effects, and manufacturing capacity to satisfy global demand remain unanswered [26]. As a result, monoclonal antibodies will continue to be a feasible COVID-19 vaccine option for the near future. Development of a vaccine needs a regulated complex process that usually takes years before it gets approved by the health authorities; but, considering the urgency of the SARS-CoV-2 pandemic, many vaccine developers have made tremendous progress in their endeavors and launched the product sooner than expected. Several of these products show excellent efficacy in a range of 90-95% in the clinical approval process. Recently, the FDA and Health Canada have given emergency authorization of those products for an early intervention because delaying immunization will have a catastrophic effect on the healthcare system. Although these vaccines appear to be safe and effective in their short study period, long-term safety and efficacy need to be evaluated.

2.2. Passive immunotherapy approaches

There has not been any specific treatment plan for COVID-19 infected patients; however, medications from different functional groups have been authorized for hospitalized patients [30]. Although vaccine administration has been ramped up in recent months the emergence of more transmissible variant strains of COVID-19 poses a threat to the long-term management of this pandemic. Many variant strains have been isolated in different parts of the world and some of these strains have the capability to spread faster compared to the native SARS-CoV-2 [31]. Because of their higher transmissibility potential SARS-CoV-2 variants can spread in a logarithmic scale [32]. A recent study shows that the vaccine is not fully effective in controlling the virus pathogenesis, particularly in severely ill patients [33]. Considering the severity of this disease other therapeutic options should be investigated to treat hospitalized patients. Antibody-based passive immunization thus seems to be a rational intervention at this moment to fight against this deadly virus [34]. With a tremendous amount of knowledge of antibody discovery over the years, such therapeutic antibodies can be either isolated from a convalescent patient or developed in a lab [35].

2.2.1. Convalescent plasma therapy (CPT)

Convalescent plasma therapy (CPT) in which neutralizing antibodies derived from a recovered patient are used to treat infected patients through plasma transfusion has been in practice for curing viral diseases for several decades. This empirical approach seems to be a viable strategy to combat the SARS-CoV-2 as antibodies from a fully recovered donor patient might be used to treat critically ill patients [36–38]. Convalescent plasma therapy (CPT) has been investigated for the treatment and investigation of other viral infections such as SARS-CoV, MERS, Ebola, and avian influenza A [39,40]. Based on previous experience with CPT SARS-CoV and MERS the early transfusion seems to be more effective [38,41]. This method could be used to increase the survival rate of critically ill COVID-19 patients at the earliest stage, as with the progress of other viral infections viremia risk increases significantly [42]. Convalescent plasma therapy may not be beneficial in treating patients with mild symptoms or for patients in the end-stage of infection; the mortality rate of end-stage patients is significantly higher because of their disease severity and damage to the vital organs. In case of mild symptoms or asymptomatic patients, convalescent plasma therapy is not necessary, and in most cases, they are self-recovered [43]. There are other factors that might influence the treatment efficacy; the titer of SARS-CoV-2 neutralizing antibodies in the CP and the collection time scale from the donor. Although the SARS-CoV-2 neutralizing antibodies titer in the donor plasma is not estimated before the transfusion, experimental evidence suggests that plasma antibodies start increasing after roughly three weeks of symptom onset and peaks at twelve-weeks. Therefore, collection of blood plasma at week 12 after the initiation of the symptoms from the donor seems to be more efficient for Convalescent Plasma Therapy [44,45].

SARS-CoV-2 survivors' CP may be a successful solution for protecting COVID-19 patients with antibody deficiencies [46]. The efficacy of CPT in COVID-19 patients with primary and secondary humoral immunodeficiency has not been fully investigated. Some case studies have confirmed its effectiveness; for example, Clark et al. reported that a 76-year-old COVID-19 patient with impaired humoral and cellular responses survived after receiving hyperimmune plasma [47]. An immunocompromised COVID-19 patient with myeloid malignancy, disseminated tuberculosis, and kidney disease was successfully treated with CP and tocilizumab in another study [48]. Several clinical trials examining the use of CPT in COVID-19 are currently underway [38,39,41] . CPT has been shown to be effective, and it seems to be a viable option for treating serious COVID-19 patients in addition to other treatment options [49]. The efficacy of CPT can differ depending on the type of microbe, its pathogenesis, and treatment protocols such as timing, dosing, and volume of administration [41].

Although CPT is well-tolerated by recipients [39], like all treatment methods, it does have some unwanted effects. CPT's most frequent side effects are transfusion-related, including chills, fever, rash, allergic reactions, circulatory overload, and hemolysis [45,48]. Other issues associated with the listed method include a shortage of plasma donors, the chance of cross-contamination, batch-to-batch instability, non-scalability, and the probability of host reaction [50]. Therefore, it seems prudent to generate monoclonal antibodies specific for SARS-CoV-2 to avoid these pitfalls.

2.2.2. Antibody-based therapies

Multiple pathogenesis steps of SARS-CoV-2 can be targeted via antibodies. SARS-CoV-2 shares a high degree of nucleotide sequence identity of 89.1% with SARS-CoV [51,52]. Therefore, previous studies on designing antibodies against SARS-CoV will be highly beneficial in developing antibodies for SARS-CoV-2 infection. Based on their functional properties monoclonal antibodies designed against SARS-CoV-2 can be classified in to in three main groups: 1) inhibition of virus

attachment and entry to the host by either targeting the virus component or the host receptors, 2) interfere with the virus replication and transcription mechanisms, 3) alteration of host immune system response (Fig. 2). Compared to CPT, antibody-based therapy has the advantage of higher neutralizing specificity, superior safety, easier application, and better scalability [53]. This can partly be attributed by the fact that most commercially developed antibodies are monoclonal typically raised or selected against single epitopes thus conferring higher immunogenicity. Some of the anti-SARS-CoV2 monoclonal antibodies developed using blood samples donated by convalescent SARS-CoV2 patients, using a methodology that has been successful in creating the antibody therapies against other viruses such as Ebola (ZMapp, REGN-EB3) and respiratory syncytial virus (palivizumab) [54,55]. From the initial panel of monoclonal antibodies obtained from convalescent serum, top candidates are selected for final production based on a set of criteria such as high potency (IC50 in the nano to picomolar range), low toxicity or side effects, and no antibody-dependent enhancement.

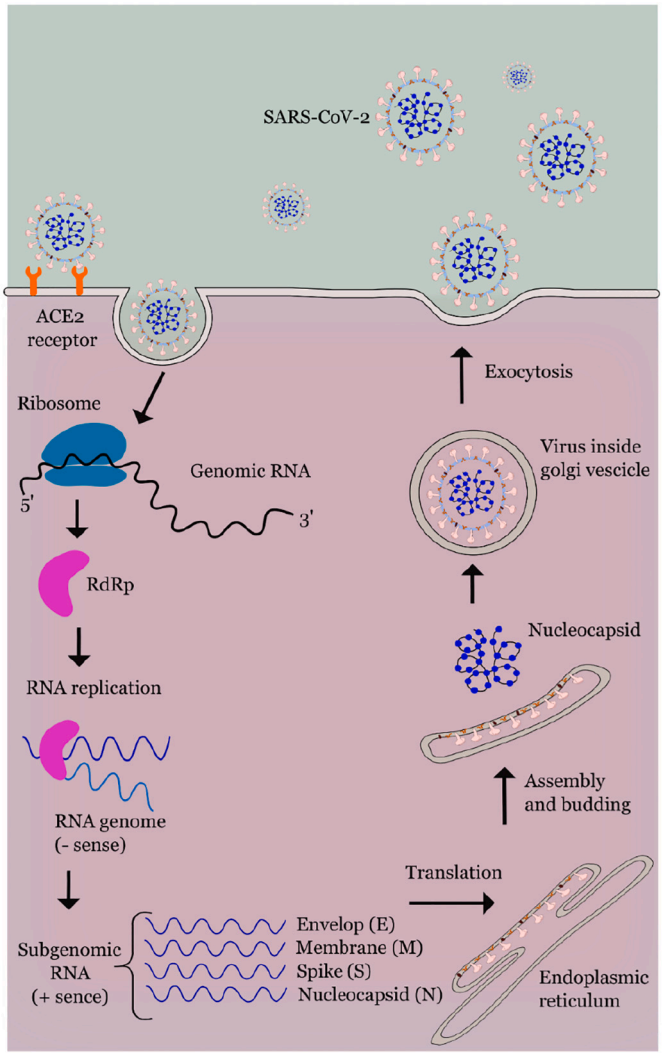

Fig. 2. The life cycle of SARS-CoV-2 in the host cells. The S glycoproteins of the virion utilizes the cellular receptor angiotensin-converting enzyme 2 (ACE2) and cellular protease TMPRSS2 (transmembrane protease serine 2) to enter target cells through an endosomal pathway. The viral RNA is uncoated and released into the cytoplasm soon after the entry of the virus into the host cell. ORF1a and ORF1ab are translated to produce pp1a and pp1ab polyproteins, which are then cleaved by viral proteases encoded by ORF1a to produce 16 non-structural proteins that assemble into the RNA replicase-transcriptase complex (RTC). Both replication and transcription of negative-sense RNAs[(-) RNA)] are carried out by this RTC complex; during the replication phase, full-length (−) RNA copies of the genome are produced and used as templates for full-length (+) RNA genomes, in the transcription process, a subset of 7-9 subgenomic RNAs, including those encoding all structural proteins, are produced through discontinuous transcription. Following the production of SARS-CoV-2 structural proteins, nucleocapsids are assembled in the cytoplasm from genomic RNA and N protein. Virion particles are formed by budding into the lumen of the endoplasmic reticulum (ER)–Golgi intermediate compartment and finally released from the infected cell through exocytosis.

3. Epitope identification in antibody-based immunotherapy

3.1. Spike protein as a primary target for antibody development

The surface spike proteins that give a crown-like appearance to the SARS-CoV-2 are the primary targets [56]. The pathogenesis process of SARS-CoV-2 begins with the attachment of the receptor-binding domain (RBD) of the spike protein to the ACE2 of the host cell [57]. Therefore, targeting the antigenic segment of the S protein through monoclonal antibodies would prevent the virus attachment to the host cell [58]. Considering the high sequence identity between SARS-CoV-2 and SARS-CoV, some of the receptor binding domain (RBD) specific antibodies of SARS-CoV can be repurposed for SARS-CoV-2 [59,60].

The spike glycoprotein is a crucial viral component that allows human coronaviruses to recognize, bind to, and enter host cells. This 180kD glycoprotein comprises two subunits namely S1 and S2; the S1 subunit binds to the ACE2 receptor of the host cell whereas the S2 subunit mediates the fusion of the virus to the host cell [58]. The SARS-CoV-2 mainly gain access to the host cell through endocytosis; PIKfyve, TPC2, and cathepsin L are critical for virus entry [61]. Spike glycoproteins from the SARS-CoV-2 (SARS2-S; 1273 residues, Wuhan-Hu-1 strain) and SARS-CoV (SARS-S, 1255 residues, Urbani strain) are structurally very similar: both bind to the human angiotensin-converting enzyme 2 (ACE2) protein [62]. However, recent investigations suggest SARS-CoV-2 exhibits a significantly higher binding affinity towards the ACE2 receptor compared to SARS-CoV. Both the spike proteins from SARS-CoV-2 and SARS-CoV share high sequence similarity, including the region consisting the receptor-binding motif (RBM) that directly contacts ACE2. Detailed sequence analysis confirms that the most variable segment in the SARS-CoV-2 is the receptor-binding domain of the spike protein (Fig. 3). The amino acids in this region that are found to be critical for binding to the ACE2 receptors are L455, F486, Q493, S494, N501, and Y505 [62]. Neutralizing monoclonal antibodies could target the spike (S) glycoproteins on the SARS-CoV-2 surface that mediate entry into host cells and prevent virus entry. Two virus-binding hotspots on the surface of ACE2 are identified for the SARS-CoV binding. Several naturally selected mutations in the SARS-CoV RBM accompany these hotspots and control SARS-CoV infectivity, pathogenesis, cross-species, and human-to-human transmissions. Since the spike proteins of SARS-CoV and SARS-CoV-2 have a similar sequence, it was recently predicted that SARS-CoV-2 also uses ACE2 as its receptor, which has been established by other studies. The transmembrane protein trimeric spikes undergo significant structural changes upon binding to its host cell receptor, angiotensin-converting enzyme 2 (ACE2), that mediates subsequent membrane fusion and virion entry [63]. The spike trimers in the prefusion isoform are broad and can take on a range of isoforms [64,65]. The prefusion trimers can be classified according to the receptor-binding domain (RBD) orientations, the closed and the open RBD conformations. The RBD of one or two of the spike monomers is surface exposed and accessible for ACE2 recognition in the open conformation (Fig. 4). On the other hand, in the closed conformation, all the three RBDs are covered by the N-terminal domain (NTD) of the spike protein. The prefusion spike trimer undergoes a structural transformation to the post fusion isoform after binding to the ACE2 receptor, in which the fusion peptide and transmembrane domains are bridged together, forming a long needle-like shape.

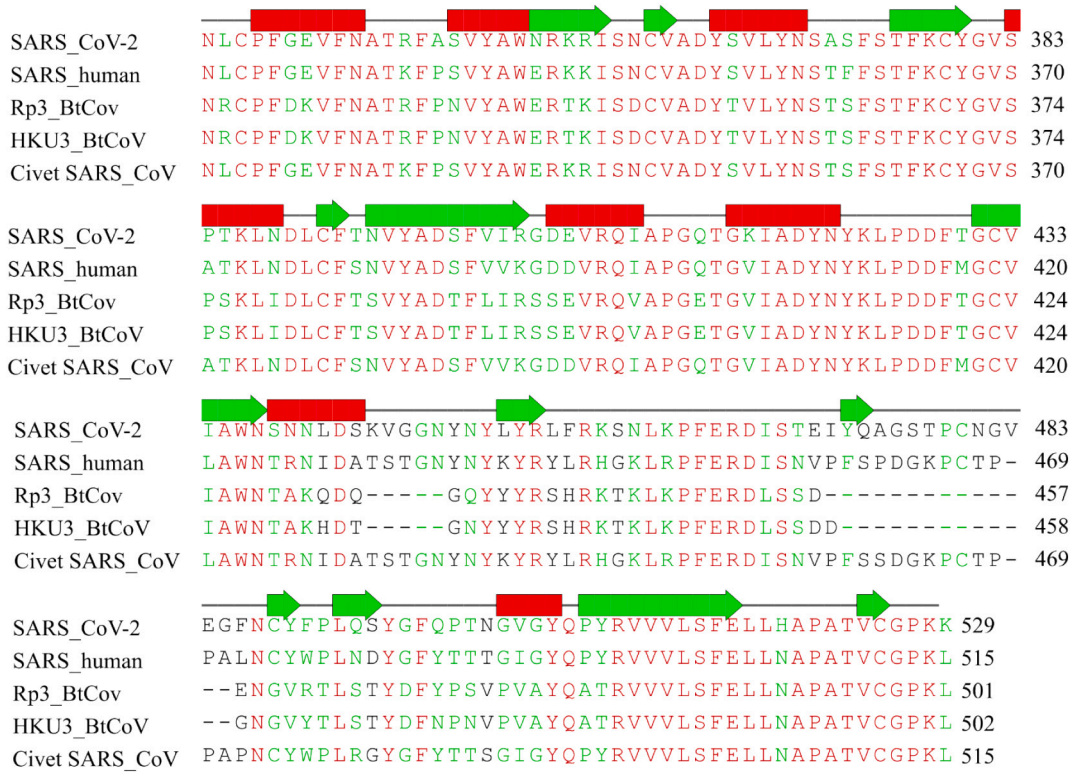

Fig. 3. Sequence alignment of the RBDs from SARS-CoV2 and SARS-like viruses. The main motifs of the ACE2-binding region in various viruses are aligned. UniProtKB/Swiss-Prot accession numbers are: P0DTC2 for human SARS-CoV-2 spike; human P59594 for SARS-CoV spike; Q3I5J5 for bat SARS-CoV spike; Q3LZX1for bat Rs3367 spike; Q3ZTF3 for civet **SARS**-CoV. Secondary structure information was derived from the human SARS-CoV-2 spike protein.

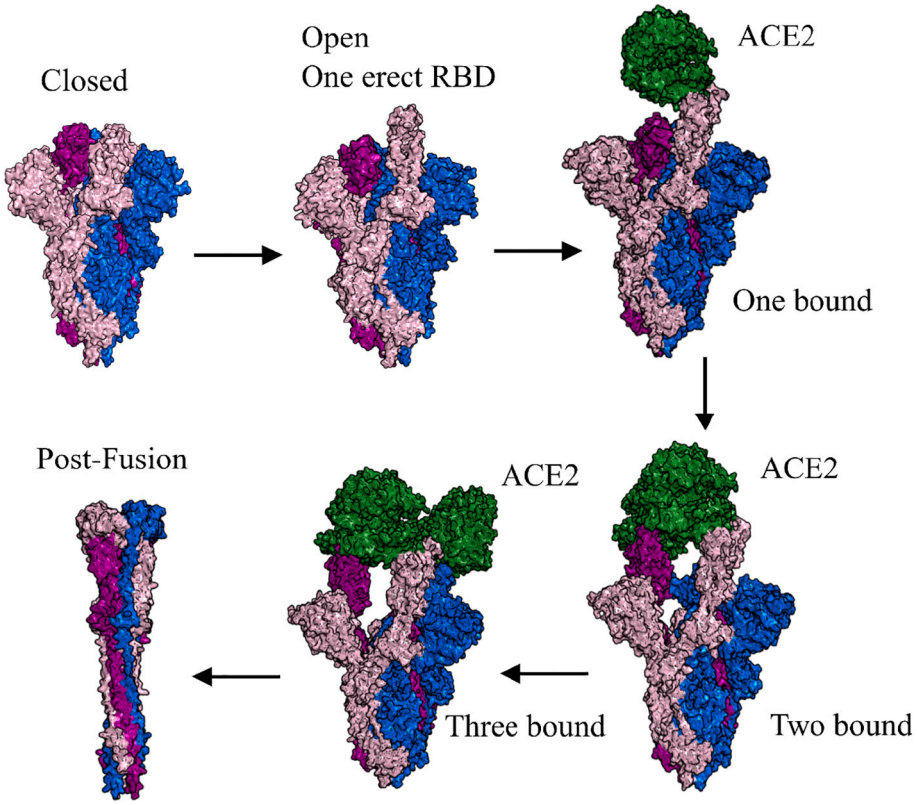

Fig. 4. The structures of the prefusion and post-fusion trimeric spike for SARS-CoV-2. Surface representation of the spike, with monomers coloured in blue, purple, and pink, and ACE2 coloured in green. Clockwise from the top, we show structures of unbound spike trimer in the closed conformation(PDB ID: VXX), one spike monomer with open unbound RBD(PDB ID: VXY), followed by sequential ACE2-binding events until reaching the fully open state with three-ACE2-bound to three spike protein monomers(PDB ID:7A94, SARS-CoV-2 spike with one ACE2 bound), (PDB ID:7A97, SARS-CoV-2 spike with two ACE2 bound), (PDB ID:7A98, SARS-CoV-2 spike with three ACE2 bound). The post-fusion state is an elongated conformation of the spike protein (PDB ID:6M3W). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Other antibody targets

Although SARS-CoV and SARS-CoV-2 share a great degree of structural homology between them, the cross-reactivity of SARS-CoV antibodies against SARS-CoV-2 are still ambiguous. These varying cross-reactivity proprieties are attributed to the differences in the spike protein structures; the C-terminal of SARS-CoV-2 RBD does not resemble much with that of SARS-CoV [66]. Additionally, an additional furin cleavage site is present between the S1 and S2 subunits in SARS-CoV-2; this site is not present in the SARS-CoV spike protein [67]. These structural characteristics may not interfere with both viruses' abilities to recognize the ACE2 receptor but may be important to clarify the differences in the affinities of the neutralizing antibodies [51,57,65]. Furthermore, a recent analysis also emphasized that the antibodies targeting the RBD are virus-specific whereas antibodies that recognize epitopes outside of the RBD are capable of cross-neutralize other virus species [68]. It has been found out that about 85.3% of antibody RBD epitopes in the SARS-CoV-2 spike were novel in comparison with those in SARS-CoV despite both share a greater overall structural homology [69]. In contrast to SARS-CoV, the receptor of the SARS-CoV-2 spike was novel; an epitope-based computational study found that 85.3% of antibody epitopes in the SARS-CoV-2 spike were novel in comparison to SARS-CoV [69]. As a result, the antibodies against SARS-CoV should be re-evaluated for use against SARS-CoV-2. F26G19, CR3022, and 47D11 were found to cross-neutralize SARS-CoV and SARS-CoV-2 when used together.

There have been several monoclonal antibodies developed to neutralize the SARS-CoV infection. An anti-S1 human monoclonal antibody 80R recognizes the conformational epitope (amino acid residues 426-492) on the S1 fragment of SARS-CoV with a nanomolar affinity [70]. Another monoclonal antibody 47D11 binds to a conserved epitope on the spike receptor-binding domain and could cross-neutralize the SARS-CoV-2 [71]. The cross-reactive nature of 47D11 indicates the possibility of targeting the conserved core structure of the S1 receptor. In a detailed analysis of cross neutralizing properties of SARS-CoV antibodies it has been observed that the m396 antibody can neutralize both SARS-CoV-2 and SARS-CoV due to the conservation of the salt-bridge and electrostatic interaction on the virus epitope [72]. However, R80 and F26G19 SARS-CoV antibodies don't interact with SARS-CoV-2 in a similar fashion; R80 is a low binding affinity antibody whereas F26G19 neutralizes SARS-CoV-2 more potently through other interactions [51]. Structural analysis of SARS-CoV-2 spike protein with the host ACE2 through cryo-electron microscopy and X-ray crystallography indicates residue range 319–591 of SARS-CoV-2 RBD as the critical region contacting the host enzyme [62]. Although the RBD remains the primary target of interest some SARS-CoV-2 neutralizing antibodies recognize other epitopes on the spike protein; S1 subunit, S-ecto domain, HR1and HR2 domains in the S2 subunit, nucleoprotein (NP), or envelope(E) protein [73–75]. Efficient cross-neutralization of SARS-CoV-2 by CR3022 interferes with the ACE2 binding of SARS-CoV-2 indicates there are binding epitopes other than RBD [57]. The HR2 domain share a sequence identity of 93% between SARS-CoV and SARS-CoV-2, and thus SARS-CoV neutralizing antibodies 2B2, 1A9, 4B12, and 1G10 that target the HR2 domain, could potently cross-neutralize the SARS-CoV-2 [76]. Another monoclonal antibody, S309, derived from convalescent SARS-CoV patients cross-neutralizes SARS-CoV-2 through recognition of a domain other than the RBD and does not interfere with the interaction with ACE2 receptor [77].

Although it is quite apparent to target the RBD of the SARS-CoV-2 spike protein to prevent host entry there have been some contrasting outcomes to this approach.

Antibody-mediated enhancement of viral entry has been based in some cases; binding of monoclonal antibody to the RBD mimics the rigid conformation of the RBD with the host receptor conducive for viral entry to the cell through receptor dependent pathways [78]. Some investigations attributed this feature to the antibody dosage and to the Fc portion of the antibody. While ACE2 has been identified as the primary SARS-CoV receptor, it may not be the necessary element for the cell-virus interaction. Other cellular factors, such as the cytoskeleton protein vimentin, have been discovered to play a role in the development of the ACE2-SARS-CoV complex [79]. As a result, surface vimentin was identified as a possible SARS-CoV target. The transmembrane adhesion molecule DS-SIGN/CD209 is primarily expressed on interstitial dendritic cells and lung alveolar macrophages [80]. It was shown that DS-SIGN also mediates the entry of SARS-CoV [81]. A humanized monoclonal antibody was produced to interfere with the interaction of DS-SIGN and intercellular adhesion molecule 3 (ICAM-3), and thus inhibit SARS-CoV entry to the cell [82]. Similar proteins may be identified regarding SARS-CoV-2. In addition to inhibiting the virus entry, antibodies can inhibit the biological activities of the virus thereby preventing its replication. Monoclonal antibodies that can target the papain-like proteases (PLpro), cysteine-like protease (3CLpro), and other functional proteins can impair viral replication inside the host cell [83]. There have been several instances of development of humanized antibodies capable of crossing the cell membrane and targeting virus replication pathways in several kinds of viruses, such as influenza, hepatitis C virus, and Ebola [54].

4. Development of monoclonal antibodies against SARS-CoV-2

There has been remarkable progress made in monoclonal antibody development in recent years. Production of monoclonal antibodies in large quantities is possible through hybridoma cell lines and through bacterial protein expression. Tremendous evolvement in antibody technology has made it possible to produce humanized antibodies through several techniques such as immunized transgenic mice (e.g. XenoMouse® or HuMAB® mice), various phage-display systems such as generating antibodies from immunoglobulin cDNA libraries in bacteria or mammalian cells, and by obtaining memory B cells of convalescent patients that are immortalized by EBV transformation [84]. Research studies of monoclonal antibodies against SARS-CoV-2 is in its infancy. Analysis of the antibodies derived from the convalescent plasma of recently recovered SARS-CoV-2 patient indicates the presence of versatile nature of antibodies. Additionally, each patient exhibits a unique bio-distribution pattern of SARS-CoV-2 neutralizing antibodies. These preliminary findings could possibly make the development of anti-SARS-CoV-2 antibodies more challenging [68]. Many neutralizing SARS-CoV2 antibodies are in the development and preclinical investigation stages, with the rest focusing on the spike protein and preventing viral entry into the host cell (Table 1). Several of these SARS-CoV-2 antibody candidates are in clinical trials, and three of them, LY-CoV555 (Eli Lilly/AbCellera), REGN-COV2 (Regeneron), and CT-P59(Celltrion), have recently received emergency authorization. Other antibodies against SARS-CoV2 in various stages of development include JS016 (Eli Lilly/Junshi Biosciences, Phase 1), TY027 (Tychan, Phase 1), BRII-196 and BRII-198 (Brii Bio/TSB Therapeutics/Tsinghua University/the 3rd People's Hospital of Shenzhen), and SCTA01 (Sinocelltech Ltd./Chinese Academy of Sciences).

LY-CoV555 (bamlanivimab), an antibody therapeutic against SARS-CoV-2 was developed jointly by AbCellera and the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID). This antibody was derived from the blood sample taken from one of the first U.S. patients who recovered from COVID-19 [85]. This is the world's first SARS-CoV-2 specific antibody therapy to enter a clinical trial for the prevention and treatment of COVID-19 in early June 2020. On November 9, 2020, Lilly was granted emergency use authorization (EUA) of LY-CoV555 for SARS-CoV-2 by the U.S. Food and Drug Administration (FDA) [86]. LY-CoV555 was found to bind to an epitope that overlapped the ACE2 binding site, with 7 of the RBD's 25 sidechains contacting ACE2. The LY-CoV555 epitope is completely accessible on both the up and down conformations of the RBD; high-resolution cryo-EM imaging of LY-CoV555 Fab complexes revealed that the LY-CoV555

Table 1
Summary of monoclonal antibodies against SARS-CoV-2.

Clinical stage	Trial ID	Product name	Sponsor	Target
EUA	NCT04427501	LY3819253 (LY-CoV555)	AbCellera/Eli Lilly	SARS-CoV-2 S protein
EUA	NCT04425629 NCT04426695 NCT04452318	REGN-COV2 (REGN10933 + REGN10987)	Regeneron/NIAID	SARS-CoV-2 S protein
EUA	NCT04525079; NCT04593641; NCT04602000	CT-P59	Celltrion	SARS-CoV-2 S protein
EUA request submitted to FDA	NCT04545060; Activ-3 study	VIR-7831/GSK4182136	Vir Biotechnol./GlaxoSmithKline	SARS-CoV-2 S protein
Phase-3	NCT04507256 NCT04625725 NCT04625972	AZD7442	AstraZeneca	SARS-CoV-2 S protein
Phase-3	NCT04429529; NCT04649515	TY027	Tychan	SARS-CoV-2 S protein
Phase-3	NCT04479644; Activ-3 study	BRII-198	Brii Bio/TSB Therapeutics/Tsinghua University/the 3rd People's Hospital of Shenzhen	SARS-CoV-2 S protein
Phase-3	NCT04479631; Activ-3 study	BRII-196	Brii Bio/TSB Therapeutics/Tsinghua University/the 3rd People's Hospital of Shenzhen	SARS-CoV-2 S protein
Phase-3	NCT04483375; NCT04644185	SCTA01	Sinocelltech Ltd./Chinese Academy of Sciences	SARS-CoV-2 S protein

Fab binds the spike protein RBD in both up and down conformations [85]. LY-CoV555 showed high safety potency in both in vitro of SARS-CoV2 infection, promoting its application as a therapeutic for the treatment and prevention of COVID-19. Following SARS-CoV-2 inoculation, prophylactic therapy with LY-CoV555 resulted in substantial reductions in viral load (gRNA) and viral replication (sgRNA) in the lower respiratory tract [87]. The drug LY-CoV555 is currently being used in clinical trials for the treatment and prevention of COVID-19 (NCT04411628; NCT04427501; NCT04497987; NCT04501978).

To battle COVID-19, Regeneron is producing REGN-COV2, a mixture of two monoclonal antibodies, REGN10933 and REGN10987 [88]. These human antibodies were developed using blood samples from recovered COVID-19 patients and humanized VelocImmune® mice. A broad and diverse array of antibodies targeting specific epitopes on the receptor-binding domain of the SARS-CoV-2 spike protein have been developed as part of this effort. Both REGN10933 and REGN10987 have a high affinity for distinct and non-overlapping epitopes on the monomeric RBD of the spike protein (Kd = 0.56 to 45.2 nM) [89]. Antiviral activity against pseudo viral particles or SARS-CoV2 with IC50 values of 1-10 pM suggests that these antibodies have a potent antiviral capacity. Treatment of this non-competing antibody combination also inhibits the production of escape mutants [90]. Regeneron started a late-stage clinical trial evaluating REGN-COV2 for the treatment and prevention of COVID-19 in late June 2020. This includes REGN-COV2's capacity to avoid infection in individuals who have had direct contact with a COVID-19 patient but are not infectious. Regeneron announced on October 7, 2020, that they had sent a submission for a EUA for REGN-COV2 to the US Food and Drug Administration (FDA), which was granted on November 20, 2020.

Celltrion Healthcare in South Korea developed CT-P59, a human monoclonal antibody (mAb) derived from a convalescent patient's peripheral blood mononuclear cells. This mAb lowers the risk of COVID-19-related hospitalization and oxygenation until Day 28, and it lowers the rate of progression to serious COVID-19 by 54% for mild-to-normal symptoms and 68% for moderate patients aged 50 and up. When compared to placebo, this antibody therapy significantly reduces the time to clinical recovery, ranging from 3.4 to 6.4 days. Based on the complex crystal structure of CTP59 Fab/RBD, CT-P59 blocks interaction regions of SARS CoV2 RBD for angiotensin converting enzyme 2 (ACE2) receptor with an orientation that differs from previously described RBD-targeting mAbs [91]. The effects of CT-therapeutic P59 have also been tested in three animal models (ferret, hamster, and rhesus monkey), with substantial decreases in virus titer and reduction of clinical symptoms [91]. As a result, CT-P59 may be a candidate for COVID-19 therapy. CT-P59's effectiveness against emerging virus mutations has been verified, and research on developing a neutralizing antibody cocktail therapy with CT-P59 has been initiated; CT-P59 mAb effectively neutralizes SARS-CoV-2 isolates, including the D614G variant. A total of 38 potent neutralizing antibody candidates against SARS-CoV-2 was identified to elicit potent neutralizing antibodies against the new emerging variants and to shorten the time duration for virus clearance. Antibody candidate No 32 effectively generated neutralizing titers against the new emerging strains in the UK and South Africa [92]. Celltrion has started developing a CT-P59-based neutralizing antibody cocktail to combat new SARS-CoV-2 forms.

AZD7442, a mixture of COV2-2196 and COV2-2130, is being developed by AstraZeneca and Vanderbilt University as a possible COVID-19 prevention and treatment combination therapy [88]. COV2-2196 uses residues in complementarity defining regions (CDRs) 2 and 3 of the heavy chain and CDRs 1 and 3 of the light chain to form an "aromatic cage" at the heavy/light chain interface. COV2-2130's composition shows that an extraordinarily long light chain CDR1 and heavy chain CDR3 interact with the RBD on the opposite side of the RBD recognized by COV2-2196 [93]. Nonetheless, both COV2-2196 and COV2-2130 demonstrated good neutralizing behavior against the native SARS-CoV-2 strains as well as the emerging variants such as E484K, N501Y, and D614G. Research analysis reveals antibody features that allow identification of the RBD and show that a combination of antibodies like AZD7442 will stop evolving variant viruses from escaping. When used separately or in combination, two noncompeting antibodies, COV2-2196 and COV2-2130, synergistically neutralised SARS-CoV-2 in vitro and protected against SARS-CoV-2 infection in mouse models and a rhesus macaque model [94]. AZD7442, is being studied in several Phase III clinical trials for post-exposure prophylaxis (ClinicalTrials.gov Identifier: NCT04625972), preventive (Identifier: NCT04625725), and outpatient care (Identifier: NCT04625725) out patient treatment (Identifier: NCT04723394 and NCT04518410) and in-patient treatment (NCT04501978) of COVID-19.

Two human antibodies (CA1 and CB6) were isolated from a convalescent COVID-19 patient using single B cell sorting and cloning techniques by researchers from the Chinese Academy of Sciences in Beijing and Junshi Biosciences in Shanghai [88]. These human antibodies have been shown to have potent neutralization activity against SARS-CoV-2 in vitro, with IC50s of 0.036 0.007 g/mL (0.24 0.047 nM) for CB6 and 0.38 g/mL (2.53 nM) for CA1 [95]. The CB6 is an ACE2 blocker that identifies an epitope overlapping with the ACE2-binding site on the RBD of the SARS-CoV-2 spike protein. To reduce the risk of Fc-mediated acute lung damage, the LALA mutation was introduced into the Fc component

of CB6 (CB6-LALA) [95]. In both prophylactic and treatment conditions, CB6-LALA was shown to prevent SARS-CoV-2 infection in rhesus monkeys. The CB6-LALA also reduced the viral titer by roughly 3 logs after four days of administration as compared to the control group. A single dose of CB6-LALA (50 mg/kg) given before SARS-CoV-2 challenge effectively protected the animals from SARS-CoV-2 infection in the prophylactic community. CB6-LALA (also known as JS016) is currently being tested in clinical trials [88].

Brii Bio, TSB Therapeutics, Tsinghua University, and the 3rd People's Hospital of Shenzhen developed BRII-196 and BRII-198 in a collaborative approach. In cell culture assays, BRII-196 can completely inhibit viral entry and neutralize live SARS-CoV-2 infection [96]. It binds to the highly conserved epitope of SARS-CoV-2 spike protein. When paired with BRII-196, BRII-198 binds to a different epitope on the spike protein and has an additive to a synergistic effect. They both have the potential to be effective drugs for the COVID-19 pandemic. In mid-July 2020, Brii Biosciences started clinical trials of these two human anti-SARS-CoV-2 antibodies. The Phase 1 trials are randomized, single-blind, placebo-controlled, single ascending dose-escalation studies of the antibodies administered intravenously to healthy adult volunteers to assess their efficacy, tolerability, and pharmacokinetics. The NCT04501978 Phase 3 trial is a master protocol that enables multiple investigational agents to be tested in adults hospitalized with COVID-19 relative to placebo.

Tychan, a Singapore-based biotechnology firm, partnered with the Singapore government to develop TY027 [97]. TY027 is being investigated for the treatment of SARS-CoV-2 infected patients to delay disease progression and speed recovery, as well as for its ability to provide temporary protection against the viral infection. This is a fully engineered human IgG that directly targets the SARS-CoV-2's spike protein. TY027 is safe and well-tolerated up to 20 mg/kg according to the preliminary results from the phase 1 clinical trial (SCT-001; ClinicalTrials.gov Identifier NCT04429529). When given to COVID-19 patients who are acutely infected, TY027 is expected to decrease disease severity. It has the potential to be used as a COVID-19 prophylaxis for high-risk contacts.TY027 is being explored for the treatment of patients with COVID-19 to slow the progression of the disease and accelerate recovery, as well as potentially providing temporary protection against infection from SARS-CoV-2 [98].

The human anti-SARS-CoV-2 antibody VIR-7831(GSK4182136) was developed by Vir Biotechnology, Inc. and GlaxoSmithKline [88]. This anti-SARS-CoV-2 monoclonal antibody was chosen for its ability to neutralize the virus in vitro, destroy infected cells, have a strong barrier to resistance, and that can achieve a high concentration in the lungs, one of the most frequent sites of infection [99]. VIR-7831 is a dual-action monoclonal antibody that was chosen for clinical development because of its ability to prevent viral entry into healthy cells while also clearing the infected cells. This antibody binds to an epitope on SARS-CoV-2 that is also found on SARS-CoV (SARS). The antibody has also shown in pre-clinical trials that it can neutralize the SARS-CoV-2 live virus by binding to an epitope on SARS-CoV-2 that is shared with SARS-CoV, indicating that the epitope is highly conserved, making escape mutants more difficult to develop [100]. VIR-7831 will be evaluated in the Phase 2/3 trial for the early treatment of COVID-19 in patients that are at high risk of hospitalization.

SCTA01 was developed by Sinocelltech Ltd. and the Chinese Academy of Sciences. It is a humanized monoclonal antibody, efficiently neutralizes SARS-CoV-2 and SARS-CoV at sub-nanomolar level concentration by engaging the spike receptor binding domain (RBD). In a human angiotensin-converting enzyme 2 mouse model, this antibody reduced SARS-CoV-2 titers in infected lungs and prevented pulmonary pathology. The Fab fragment of SCTA01 recognizes that the spike RBD was in an open conformation [101]. This interaction inhibits SARS-CoV-2 from binding to its host cell receptors. Epitope analysis of neutralizing antibodies against SARS-CoV and SARS-CoV-2 showed a significant number of cross-protective epitopes. NCT04483375 is a Phase 1, first-in-human, randomized, double-blinded, placebo-controlled, single ascending dose study of SCTA01 in healthy Chinese subjects.

5. Outlook for immunotherapy development

The SARS-CoV-2 pandemic has resulted in unprecedented global health and economic losses, and the crisis is far from under control. Public health systems around the world, particularly those of the most developed nations, have become overwhelmed by a vast number of critically ill patients in a brief span of time, and thousands of lives have been lost because of unpreparedness and divisive political decisions. While multiple vaccine candidates have been accepted for COVID-19, vaccine delivery and the emergence of new variant SARS-CoV-2 remain significant challenges. While the vulnerable population (e.g., the elderly or immunocompromised) can benefit the most from the vaccines, there are no care options available for the treatment of critically ill patients. Finding monoclonal antibodies for COVID-19, in addition to vaccine discovery, is crucial to win the battle against this pandemic.

Several monoclonal antibodies targeting various epitopes on the SARS CoV-2 spike protein are being investigated for COVID-19 prevention and treatment. The combination of potent antibodies targeting the RBS and specific monoclonals targeting conserved regions within the SARS CoV and SARS CoV-2 spike proteins can improve treatment effectiveness by preventing the emergence of resistant viral variants. Preclinical studies in various animal models indicate that using anti-SARS CoV-2 antibodies prior to exposure could prevent or at least reduce disease severity in people at high risk of infection (i.e., people at nursing facilities, confirmed case householders, health care workers, etc.). These antibodies can also be given early during COVID-19 infection to patients who are at a high risk of contracting a serious disease, such as the elderly or people with pre-existing medical conditions. Several clinical trials are currently ongoing to evaluate the effectiveness, tolerability, PKs, and efficacy of anti-SARS-CoV-2 antibodies in both prophylactic and therapeutic environments. But apart from the advent of virus resistance, another significant major obstacle to the use of these antibodies in large scale clinical settings are the high cost of manufacturing vast quantities of these antibodies. Given the severity and infectivity of this virus on a global scale, understanding the pathophysiology of disease and the response of the host immune system is crucial in designing better therapeutic products.

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